Drug Delivery—Pulsatile Systems

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INTRODUCTION

Historically, extended release dosage forms were developed, which release the drug continuously over longer periods of time. These dosage forms offer many advantages, such as the nearly constant drug levels at the site of action and therefore minimization of peak-trough-fluctuations, reduced frequency of administration, and an improved patient compliance. In recent years, pulsatile release systems have gained increasing interest. Ideally, with a pulsatile system, the drug is released rapidly and completely after a defined lag time of no drug release (Fig. 1A). Alternative terms used to describe pulsatile release are delayed or sigmoidal release. Besides one-pulse systems, multipulse systems release the drug in subsequent pulses.[1] The application of pulsatile release systems can be advantageous to adapt a drug therapy to chronopharmacological needs or to target a drug to a specific site in the gastrointestinal tract (GIT), e.g., to the colon.

Pulsatile drug delivery systems (DDS) can be classified in site-specific and time-controlled systems. Drug release from site-specific systems depends on the environment in the GIT, e.g., on pH, presence of enzymes, and the pressure in the GIT. In contrast, time-controlled DDS are independent of the biological environment. The drug release is controlled only by the system. Time-controlled pulsatile delivery has been achieved mainly with drug-containing cores, which are covered with release-controlling layers. The cores serve as reservoirs, which protect the core from the environment, e.g., water, acidic pH, and enzymes, until the drug is released after the lag phase. The coatings can erode/dissolve, rupture, or alter their permeability at the required time. Alternatively, capsular-shaped cores can be combined with release-controlling plugs. These strategies to release drugs in a pulsatile manner are reviewed in detail in this article.

CHRONOPHARMACOLOGY OF DRUG EFFECTS

The dependence of several diseases and body function on circadian rhythms is well known. A genetic control of a ''master clock'' located in the nucleus suprachiasmaticus was recently proposed.[2]

A number of hormones, such as renin, aldosterone, or cortisol, show distinct daily fluctuations.[3] Circadian rhythms in the onset and extent of disease symptoms were observed, including diseases such as bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer disease, and hypertension.[4]

The incidence of asthmatic attacks increased during the early morning hours with a maximum at 4 A.M.[5] (Fig. 2). A treatment based on a theophylline controlled release dosage form resulting in a constant drug plasma level would not be optimal. Therefore a therapeutic scheme taking into account diurnal variation should be more effective. This could be realized by a pulsatile dosage form, taken at bedtime with a programmed drug release in the early morning hours.

Circadian effects were also observed for the pH and acid secretion in the stomach. Despite treatment of patients with a continuous infusion of famotidine, a H_2 antagonist, the pH in the stomach showed diurnal fluctuations between pH 7 and pH 2–3.[6] Therefore a constant blood level, as obtained with a drug infusion and possibly achieved with conventional controlled drug delivery systems, does not always lead to a constant pharmacological effect. Similar effects were observed for the gastric pH in ranitidine-treated patients.[7] Another example for the need of chronopharmacological adaptation is the treatment of pain in a study with patients suffering from postoperative pain. The analgesia requirements followed a diurnal rhythm with peaks at 9 A.M. and 8 P.M.[8]

Chronopharmacology can affect the drug therapy in two ways, either in daily variations in pharmacodynamic effects or in pharmacokinetics.[9] Many drugs were studied with respect to their pharmacokinetics and chronopharmacology, including analgesics, anticancer drugs, antibiotics, psychoactive drugs, local anesthetics, antiasthmatics, anticonvulsants, and beta-blockers.[10] Beta-receptor blocking agents reduced ischemic events mainly during the morning hours.[11]

All body functions involved in absorption, distribution, and elimination of drugs can be dependent on circadian rhythms. For example, the gastric emptying time of solids

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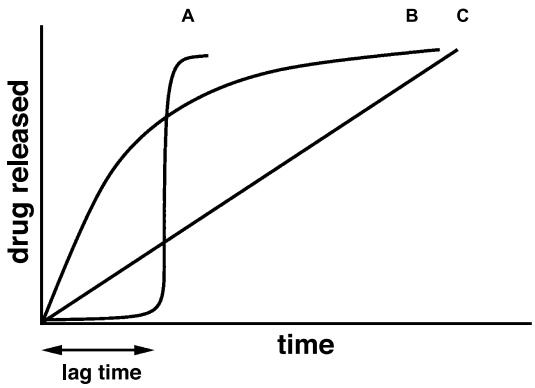

Fig. 1 Drug release profiles: (A) pulsatile, (B) and (C) conventional extended release.

is faster in the morning than in the afternoon.[12] Blood perfusion of the gastrointestinal tract was also found to be higher during early morning hours, which could affect the absorption via passive diffusion.[13,14] Especially for lipophilic drugs, the time of maximum plasma concentration, t_{max}, may decrease and maximum plasma concentration, c_{max}, may increase when applied in the morning hours.

These findings lead to the requirement of a time-programmed therapeutic scheme, whereby the drug is at the site of action at the right time in the required amount. This can be realized with pulsatile drug delivery systems.

SYSTEMS WITH ERODING OR SOLUBLE COATINGS

Most pulsatile delivery systems are reservoir devices coated with a barrier layer. The barrier dissolves or erodes after a specified lag time, after which the drug is released rapidly from the reservoir core. In general, the lag time prior to drug release can be controlled by the thickness of the coating layer.

Various lag times have been achieved with press-coated tablets, where the press-coated barrier layer consisted of a mixture of a soluble polymer, hydroxypropylmethyl cellulose (HPMC), and different water-insoluble polymers, such as ethylcellulose, Eudragit® RS, or polylactic acid in different ratios.[15] The release medium permeates through the coating and then results in disintegration of the tablet, whereby the lag time prior to disintegration decreases with increasing proportion of the water-soluble polymer.

The Chronotopic® system (Fig. 3) consisted of a core tablet containing the drug and a HPMC layer, optionally coated with an outer enteric coating.[16–19] The lag time prior to drug release was controlled by the thickness and the viscosity grade of the HPMC layer. After erosion or dissolution of the rubbery HPMC layer, a distinct pulse was observed. To avoid retarding effects in the drug release phase, the thickness as well as the viscosity grade of the HPMC layer should be limited.[20] The system probably works best for poorly water-soluble drugs. Highly water-soluble drugs could possibly diffuse through the swollen HPMC layer prior to complete erosion. In addition to core tablets, this principle was applied to hard and soft gelatin capsules.[21] The coating was applied by spraying an aqueous solution of HPMC (Methocel® E50) onto the capsules up to a weight gain of 20%. The lag time of coated capsules was longer than that of tablets at the same coating level. This was explained by the lack of disintegration power of the capsules, when compared to the coated tablets. One problem of the coated tablets was the attrition of the swollen polymer from the edges during dissolution test; this would also lead to shortened erosion rates.

The following examples describe delivery systems, whereby an impermeable, insoluble layer protects several

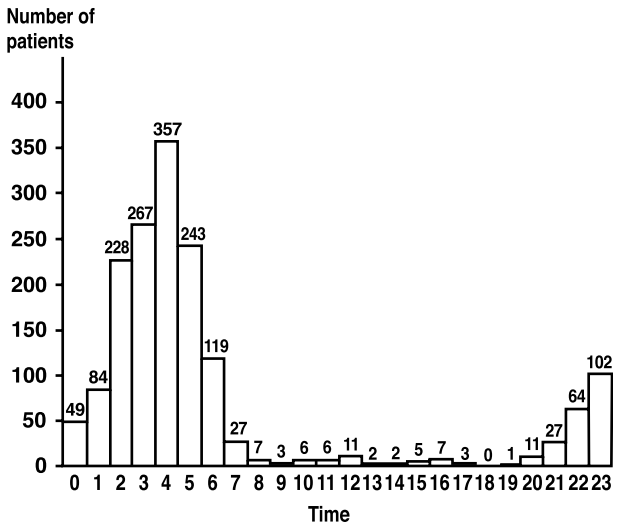

Fig. 2 Incidence of asthmatic attacks in about 1600 patients during a 24-hr cycle. (From Ref. [5].)

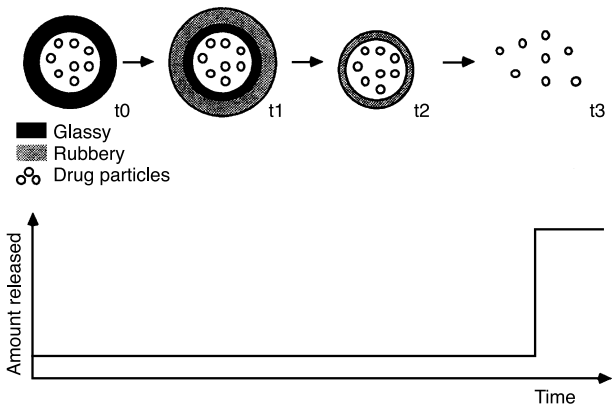

Fig. 3 The Chronotopic® system. (From Ref. [18].)

sides of the system from the dissolution medium and the drug release therefore occurs only from one side of the system.

Lippold and Möckel proposed a prototype, which consisted of a three-layer HPMC tablet, containing, from the outside to the inside, an immediate release layer, an intermediate drug-free layer, and an inner drug-containing layer (second pulse dose of drug).[22] A specially designed holder, a tight-fitting metal mould, was used to allow only one surface to come into contact with the release medium. The hydrophilic matrix eroded continuously, first releasing the drug from the immediate release layer, followed by a period of no drug release (the length of which was controlled by the thickness and therefore the erosion time of the intermediate drug-free HPMC layer) and then the second drug release pulse from the inner layer. The release profile showed a sharp increase in the beginning (first pulse; immediate dose from the top layer released), followed by a lag time, and again a drug release phase (second pulse). The lag time increased from 2.5 to 6.5 hr with increasing thickness of the HPMC layer from 1.44 to 2.87 mm. The HPMC swelled and formed a gel-like layer, thus reducing the release rate of the second pulse. This system was suggested as a prototype for a buccal tablet because of the limited transit time of a solid dosage form through the stomach and the small intestine. A buccal application supposedly would overcome this limitation.

For a final dosage form, a coating for the three sides of the system is still needed in order to overcome the need of the metal mould, which was used during the in vitro tests.

A release pattern with two pulses was obtained from a three-layer tablet consisting of two drug-containing layers, separated by a drug-free gellable polymeric barrier layer.[23,24] The three-layer tablet (Fig. 4) was coated on three sides with an impermeable coating (labeled d), consisting of ethylcellulose. Upon contact with dissolution fluids, the initial dose incorporated into the top layer (a) was released rapidly from the uncoated tablet surface. The second pulse was obtained from the bottom layer (c) after the gelled barrier layer (b) was broken by expanding disintegrants present in the bottom layer. The superdisintegrants were cross-linked polyvinylpyrrolidone (crospovidone, Polyplasdone® XL) and sodium starch glycolate (Primojel®). The lag time could be controlled by the choice of the gelling materials (HPMC types with different molecular weight). However, the drug dissolution period after the lag time was quite long due to the loss of swelling efficiency of the disintegrants present in layer (c), which slowly absorbed moisture during the slow gelation of the barrier.[25] Two distinct plasma peaks obtained in vivo (1 hr and 4.5–5 hr after administration) corresponded to the in vitro results (immediate release and a second dose released after 40 min). The deviation between in vitro and in vivo lag time for the second dose was not explained. The main drawback of this dosage form was the complicated manufacturing procedure, including the coating process. The coating step had to avoid the coating of one side (release side) of the tablet, which was obtained by manual coating with a special designed tablet holder. The design of this dosage form has been improved by the application of a press-coating procedure (instead of spray-coating) using a high viscosity HPMC grade.[26] The obtained lag times ranged from 2 to 3 hr for diclofenac, tested in deionized water, and from 2 to more than 10 hr for ibuprofen, tested in pH 7.5 medium. Although the composition of the system was the same, the ibuprofen-containing tablet showed longer lag times. The authors explained this observation with the use of different dissolution media.

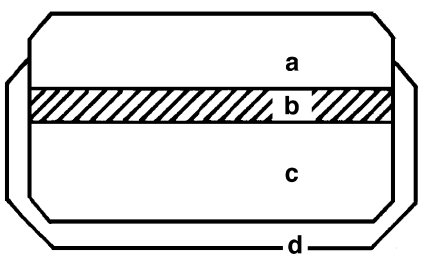

Fig. 4 A three-layer pulsatile system. (From Ref. [25].)

Press-coated tablets were produced on modified rotary tablet machines using special tools with hollow punches, where first an inner tablet was formed and then the outer shell was compressed in the same die (''tablet-within-a-tablet'').[27]

Another dosage form with an erosion-controlled lag time had a drug-containing core, which was incorporated into a compressed, hollow cylinder consisting of hydroxypropyl cellulose (HPC).[28] The flat surfaces of the tablet were coated with an impermeable polymer, poly(ethylene vinyl acetate) (Fig. 5). The delivery system was prepared by hand: a hole was drilled into a tablet to obtain the hollow matrix, the inner drug core was placed into this hole, and the system was coated by hand on the two flat base surfaces. This preparation would be quite complicated for large-scale manufacturing, and the use of a nonapproved polymer and benzene as a coating solvent would limit the application of this system. Lag times between 6 and 11 hr were achieved with either a fast drug release after the lag time (using microcrystalline cellulose or lactose in the core) or sustained release (with HPC in the core). The lag time increased with increasing thickness of the matrix cylinder. Lactose-containing cores developed an internal osmotic pressure, leading to a fast separation of the coating from the core. Thus drug was delivered before complete erosion of the outer HPC matrix. On the other hand, microcrystalline cellulose-cores had no osmotic effect, coating separation did not

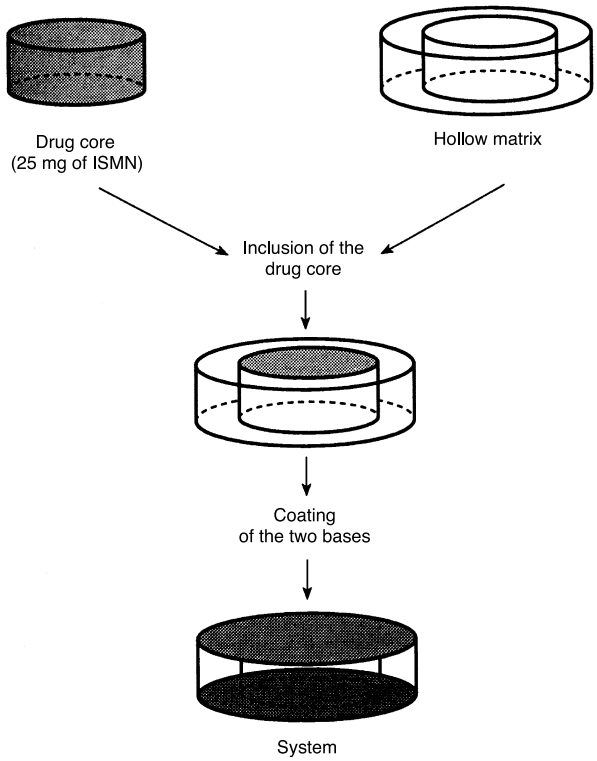

Fig. 5 Eroding system with hollow cylinder and coated surfaces. (From Ref. [28].)

occur, and the lag time was longer. The complete erosion of the matrix was necessary to release the drug.

The lipid barrier of the Time Clock® system, containing carnauba wax and beeswax, eroded or was emulsified into aqueous media because of incorporated surfactants (polyoxyethylene sorbitan monooleate).[29] The lag time increased with increasing coating thickness and was independent of the environmental pH. In vivo assessment with gamma-scintigraphy of an enterically coated Time Clock® system was in good agreement with the in vitro predicted data with regard to the lag time.[30] When the viscosity of the dissolution medium of the in vitro test was raised to 120 cps, the lag time was prolonged to the same value as obtained with in vivo data. The advantage of this system was its ease of manufacturing without the need of special equipment. However, controlled release delivery systems based on lipids may have a high in vivo variability (e.g., food effects).

SYSTEMS WITH CHANGED MEMBRANE PERMEABILITY

The permeability and water uptake of Eudragit® RS or RL [chemical name, poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride)], can be influenced by the presence of different counterions in the release medium.[31] It was found that theophylline was released faster from Eudragit® RS-coated pellets, when succinic, acetic, glutaric, tartaric, malic, or citric acid are present in the release medium.[32] Increased permeability was explained by the higher hydration of the film, also expressed as the ''free volume.''

Several delivery systems with sigmoidal or pulsatile release patterns were derived on this ion exchange. The sigmoidal release system (SRS) consisted of pellet cores, containing drug and succinic acid, coated with Eudragit® RS.[33] The lag time was controlled by the rate of water influx through the coating. The water then dissolved succinic acid and the drug inside the core, and the acid solution increased the drug permeability of the hydrated polymer film by interacting with the quaternary ammonium groups.

In a similar system, theophylline and sodium acetate, acting as the permeability modifying salt, were layered on sugar pellets, followed by coating with Eudragit® RS30D.[34] The lag time increased with increasing thickness of the outer membrane. The slope of the drug release phase was independent of the thickness but was influenced by the amount of the salt in the system.

The release profile of systems based on permeability changes appeared to depend strongly on the physicochemical properties of the drug and its interaction with the membrane. A pulsatile release profile may be obtained for some particular drug molecules in a specific formulation but cannot be generally applied to all drugs.

RUPTURABLE SYSTEMS

The other class of reservoir-type pulsatile systems is based on rupturable coatings in contrast to the swellable/erodible layers of the previous section. The drug is released from a core (tablet or capsule) after rupturing of a surrounding polymer layer, caused by a pressure build-up within the system. The pressure necessary to rupture the coating can be achieved with gas-producing effervescent excipients, an increased inner osmotic pressure or swelling agents, such as cellulose ethers, polysaccharides, or superdisintegrants.

Drug-containing tablets with an effervescent mixture of citric acid and sodium bicarbonate coated with ethylcellulose resulted in a pulsatile release after rupturing of the coating, which was caused by the carbon dioxide development after water penetration into the core.[35] The rupturing strongly depended on the mechanical properties of the coating layer: highly flexible films, such as Eudragit® RS, with high elongation and low elastic moduli, ruptured after a certain lag time as a consequence of the effervescent reaction but left only small fissures

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within the film. Therefore the drug release was prolonged and not immediate after the lag time. Using a mechanically weaker and nonflexible film, such as ethylcellulose, plasticized with 20% w/w DBS, the drug release was sigmoidal and reproducible (Fig. 6). The lag time before drug release increased with increasing coating level. Moreover, the disintegrant properties of microcrystalline cellulose, which was primarily used as a filler, supported the film rupturing.

Osmotic pressure was the mechanism of a rupturable dosage form, which was proposed by Baker in 1976.[36] The core tablet, which contained a drug and a disintegrant, was coated with cellulose derivates such as ethylcellulose or cellulose acetate. The core protection was defined as the time until the coating ruptured and the drug was released.

Another system was based on a swelling core tablet and a surrounding coating consisting of a combination of hydrophobic and hydrophilic polymers.[37] The insoluble hydrophilic polymer, such as calcium pectinate or calcium alginate, was dispersed in the coating and served as a channel-former in order to control the water penetration. The core contained a swelling, but water-insoluble polymer, a hardness enhancer (microcrystalline cellulose), and a disintegrant to achieve a fast disintegration after the membrane burst.

Also, soft and hard gelatin capsules could be coated with a swelling layer followed by coating with a rupturable polymeric layer[38] (Fig. 7). Superdisintegrants, such as Ac-Di-Sol® (croscarmellose sodium) or low-substituted hydroxypropyl cellulose (L-HPC), were used as swelling substances, which resulted in a film rupture followed by a rapid drug release. Ethylcellulose or cellulose acetate forms the outer rupturable polymeric membranes. The lag time was controlled by the composition of

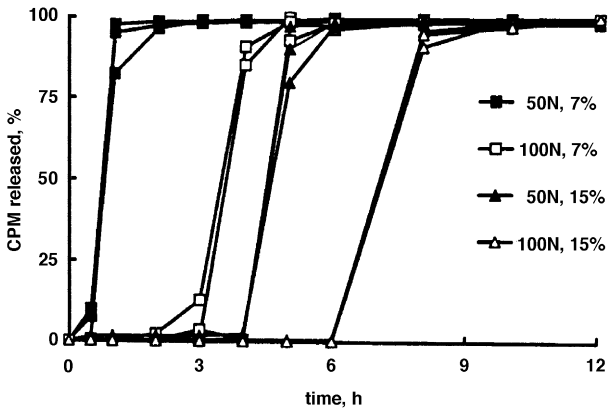

Fig. 6 Pulsatile drug delivery system based on coated effervescent cores—influence of the coating level (7% and 15% w/w) and hardness (50 and 100 N) on the drug release/lag time (coating, EC/DBS; core, 30%, w/w, effervescent agents, microcrystalline cellulose). (From Ref. [35].)

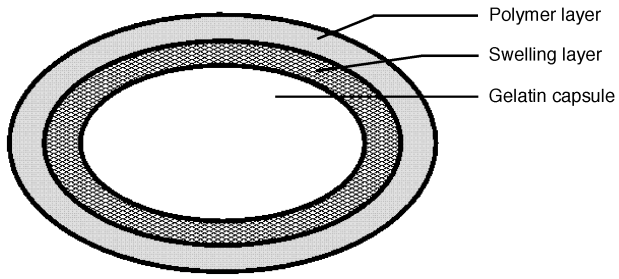

Fig. 7 Capsule-based rupturing pulsatile delivery system. (From Ref. [38].)

the outer polymer layer. Water-soluble polymers such as HPMC increased the permeability and therefore reduced the lag time. The advantage of these capsule-based systems was that both solid and liquid drug formulations could be delivered.

The systems described above are single unit systems. The rupturing of the outer coating of the individual units of a multiple unit dosage form can be induced by the same principles as described for single unit systems.

Multiparticulate drug delivery systems (e.g., pellets) have various advantages, when compared to single unit dosage forms.[39] These advantages include a reproducible and generally short gastric residence time, no risk of dose dumping, and the flexibility to blend pellets with different compositions or release patterns. However, the potential drug loading of a multiparticulate system is lower because of the proportionally higher need for excipients (e.g., sugar cores).

The time-controlled explosion system (TES) was a multiparticulate system, whereby the drug was layered on an inner core, followed by a swellable layer (e.g., hydroxypropyl cellulose) of optimal thickness (at least 180 μm) and an insoluble polymeric top layer (e.g., ethylcellulose).[40–43] Upon water ingress, the swellable layer expanded resulting in film rupturing with subsequent rapid drug release. The release was described to be independent of the environmental pH and drug solubility. The lag time increased with increasing coating level and higher amounts of talc or lipophilic plasticizer in the coating, and the release rate increased with increasing concentration of the osmotically active agents. In vivo studies of the time-controlled explosion system, which had an in vitro lag time of 3 hr, showed first drug blood levels after 3 hr and maximal blood levels after 5 hr.[44]

A combination of osmotic and swelling effects was used in the system developed by Amidon and Leesman.[45] The permeability-controlled systems consisted of a core, containing an osmotically active substance, a swelling substance, and the drug. NaCl and sorbitol were used as osmotic substances and Na carboxymethyl cellulose as the swelling material. These cores were coated with an

insoluble, semipermeable polymer, such as cellulose acetate. The time T_P, when the insoluble film ruptured, was described by the following equation:

$$T_P = \frac{V_e^* + V_d}{A \cdot a \cdot L_P \cdot \Delta\pi}$$

where T_P represented the time until film rupture (lag time), V_e^* was the volume, to which the tablet has to be expanded for film break, V_d was the displaceable volume inside the core, A was the surface area of the film, a was a constant, L_P was the water permeability of the film, and $\Delta\pi$ was the osmotic pressure difference across the film. The constant a was

$$a = \frac{\Delta r^*/r_0}{e^*}$$

where Δr^* was the critical radius increase, r_o was the initial radius of the unit, and e^* was the critical strain. This model was based on the following assumptions: the units (tablets, pellets) have a spherical shape, the thickness of the film and the osmotic pressure difference are constant, and the values of the critical stress and strain for film rupture do not change. In practice, the changing mechanical properties of the film, the changing permeability, and weak points (defects) of the film would have to be considered.

Chen has proposed a system with a core, containing an osmotically active substance (NaCl) and the drug, which was coated by an insoluble, permeable membrane.[46] The coatings included different types of polyacrylate-polymethacrylate-copolymers (Eudragit® NE30D, Eudragit® RS30D) and magnesium stearate, which reduced the water permeability of the membrane, thus allowing the use of thinner films for long lag times. Otherwise, thicker films had to be used, which were more difficult to rupture.

The lag time of a similar system was controlled by the addition of an enteric polymer to the surrounding insoluble membrane polymer (e.g., ethyl cellulose). The enteric polymer, poly(methacrylic acid-methylmethacrylate) copolymer (Eudragit® S) or hydroxypropyl methylcellulose phthalate (HPMCP), did not dissolve in the acidic pH of the stomach but dissolved in the small intestine, thus weakening the membrane and resulting in rupturing after a predetermined time. Expanding of the core upon water ingress was achieved by the presence of Explotab® (starch glycolate), a swelling substance. Again, the inclusion of water-insoluble agent (magnesium stearate) in the outer membrane resulted in thinner, less permeable films with better rupturing properties.[47]

An osmotically active, drug-containing pellet core has been coated with cellulose acetate, a semipermeable polymer, which is permeable for water but impermeable for drugs.[48,49] The lag time increased with increasing coating level and higher amounts of talc or lipophilic plasticizer in the coating, and the release rate increased with increasing concentration of the osmotically active agents. The addition of osmotically active salts, such as sodium chloride, was necessary to achieve a pulsatile release. Otherwise, the release was extended after the lag time because of the lower degree of core swelling, which resulted in only small fissures and not in a complete rupturing of the coating.

Heng et al. investigated multilayered pellets, containing neutral core pellets, an inner drug layer, an intermediate HPMC layer (swelling layer) and an outer insoluble diffusion layer, consisting of Eudragit® RS. The addition of sodium chloride to the HPMC layer decreased the rate of swelling and thus delayed the bursting of the pellets.[50] This phenomenon was first unexpected because of osmotic effects of the salt, which should promote water uptake. The longer time until rupturing was explained by the competition between sodium chloride and HPMC for the imbibed water.

A theoretical approach to calculate the burst time from an osmotically active spherical capsule, which depended on the initial radius, wall thickness, osmotic pressure of the contents, and the material of the capsule, has been presented.[51] This approach assumed that the spherical core increases in size upon osmotic water influx, leading to an elongation of the membrane until a certain yield stress is reached to rupture it. The rate of volume increase was described by the following equation:

$$\frac{dV}{dt} = D\frac{A}{l}(\Pi_0 - p)$$

where dV/dt was the rate of volume increase, D the dialysis permeability through the wall, A the area of the sphere, l the wall thickness, Π_0 the osmotic pressure difference across the wall, and p the internal pressure of the sphere.

The dimensionless values, $N_1 = \frac{Y}{M}$ and $N_2 = \frac{\Pi_0 r_0}{2Ml_0}$ (whereby Y was the yield stress at which the sphere bursts, M was Young's modulus of elasticity, r_o the initial radius, and l_0 the initial wall thickness), were derived from the volume of a sphere and Hook's law for elastic materials. N_1 determined the radius, at which the spheres burst, and is the ratio of the material properties, yield stress (Y), and Young's modulus, a value for the stiffness, (M). N_2 determined the initial expansion rate. It was concluded that the dimensionless burst time, t_b^*, increases with increasing N_2. When $N_2 > 2N_1$, the burst time t_b^* is proportional to l_0. But if $N_2 < 2N_1$, the bursting time becomes sensitive to the other values.

Increased permeability and decreased wall thickness, concomitant with appropriate mechanical membrane properties, would lead to a faster water influx and shorter lag times of such an expanding system.

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CAPSULAR-SHAPED SYSTEMS

Several single unit pulsatile dosage forms with a capsular design have been developed. Most of them consist of an insoluble capsule body, which contains the drug, and a plug, which prevents drug release during the lag phase. Mechanisms of plug removal include dissolution, erosion, or induced pushing-out of the plug by swelling or osmotic pressure.

The Pulsincap® system consisted of a water-insoluble body (hard gelatin capsule coated with polyvinyl chloride), filled with the drug formulation.[52,53] The capsule half was closed at the open end with a swellable hydrogel plug. Upon contact with dissolution media or gastrointestinal fluids, the plug swelled and pushed itself out of the capsule after a lag time, followed by a rapid release of the capsule content (Fig. 8). The lag time prior to the drug release was controlled by the dimension and the position of the plug. In order to assure a rapid release of the drug content, effervescent agents or disintegrants could be included in the drug formulation, in particular, with water-insoluble drugs. Studies in animals and healthy volunteers proved the tolerability of the formulation (e.g., absence of gastrointestinal irritation).[54] In order to overcome the

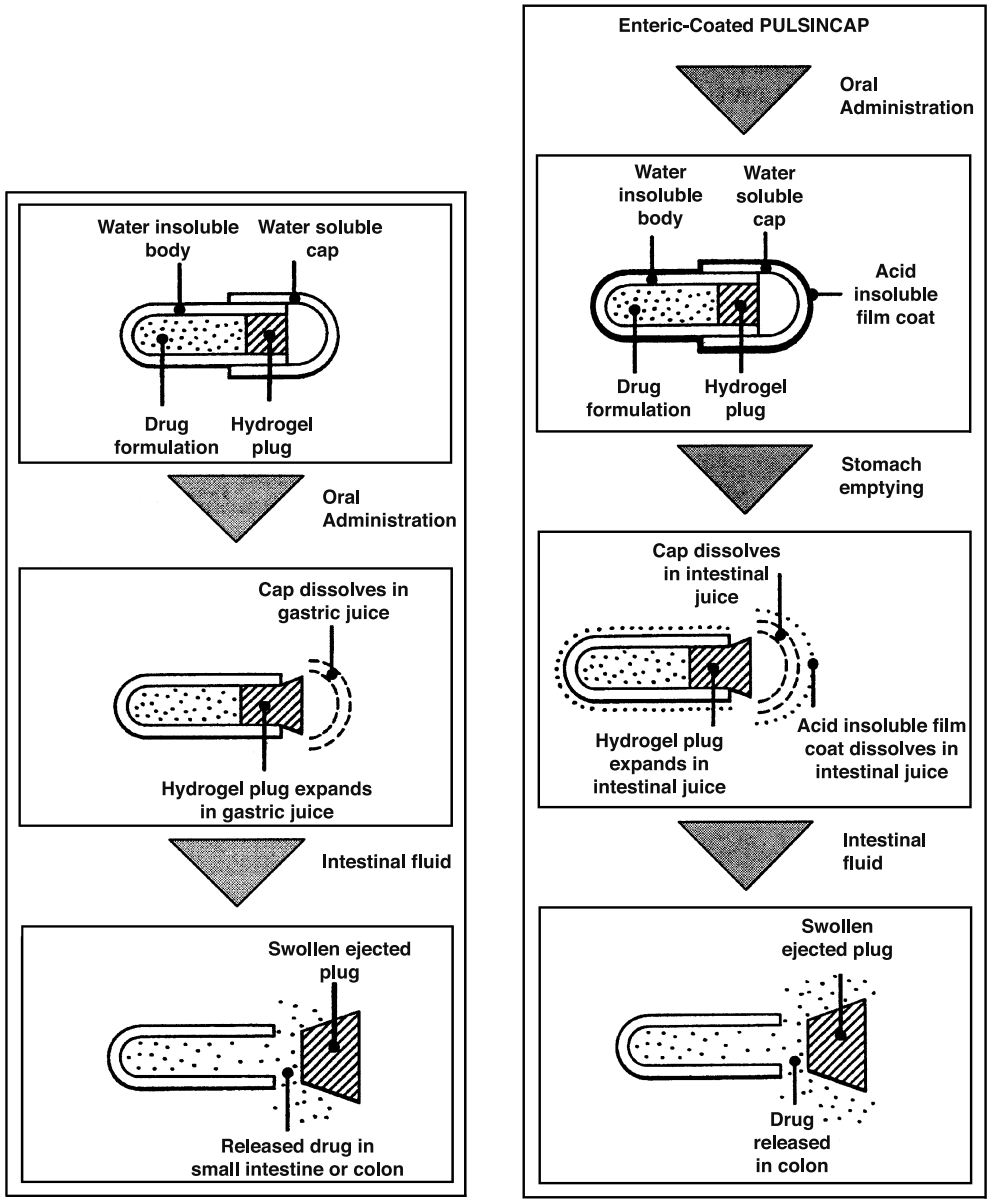

Fig. 8 The Pulsincap® system. (From Ref. [51].)

potential problem of variable gastric residence time of a single unit dosage form, the Pulsincap® system was coated with an enteric layer, which dissolved upon reaching the higher pH regions of the small intestine. This allowed a more precise control of the drug release after passage of the stomach, because the transit time in the intestinal tract is less variable.[55,56] The major drawbacks of the Pulsincap® system, which led to the withdrawal of commercial activities with this system, were the complicated manufacturing process, reproducibility problems, and the use of a plug material, a cross-linked polyethylene glycol based polymer, which has not been approved in pharmaceutical products.

As an alternative to swellable, cross-linked plugs, erodible plugs have been investigated for Pulsincap-like systems (Fig. 9). The tablet-shaped plugs can be produced by compression of a water-soluble, swellable polymer, such as HPMC, PVA, or polyethylene oxide.[57] After contact with gastrointestinal fluids, the polymer plugs swelled quickly, forming a gel, followed by a transition into a sol and a subsequent period of erosion. The swelling polymer could also be combined with soluble low-molecular weight excipients, e.g., lactose, to reduce the lag time.[58] In general, the lag time was adjusted by the choice of the molecular weight of the erodible polymer and by the thickness of the plug.

Plug degradation could also be achieved by enzymes being directly incorporated into the plug.[59] In an example, plugs containing pectin, a natural polysaccharide, were degraded by pectinolytic enzymes, whereby the lag time of the system was controlled by the ratio of pectin to enzymes (Fig. 10).

Besides compression, erodible plugs were formed by a congealing method with melts of saturated polyglycolyted glycerides (Gelucire®) or glyceryl monooleate (Myverol®).[57]

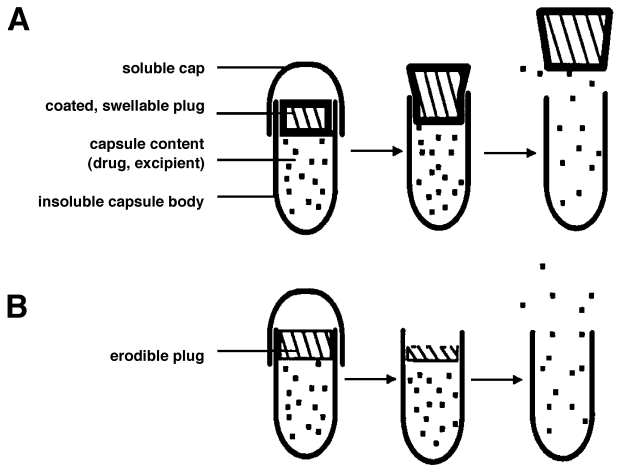

Fig. 9 Capsular-shaped pulsatile drug delivery system, consisting of an impermeable capsule body and (A) a swellable, insoluble coated plug and (B) an erodible plug. (From Ref. [56].)

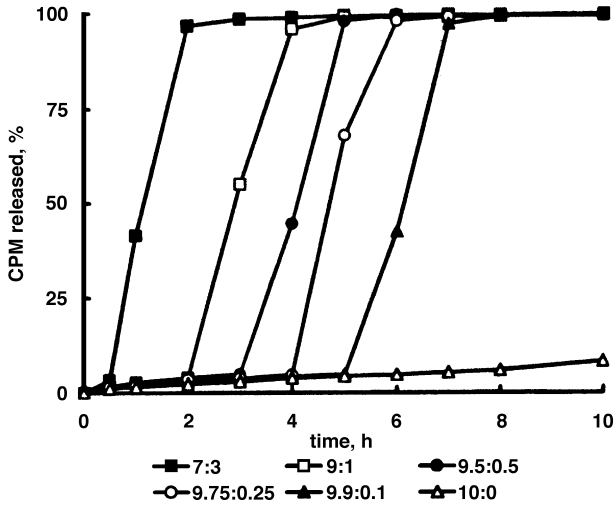

Fig. 10 Chlorpheniramine maleate (CPM) release as a function of the pectin/enzyme ratio within the plug. (From Ref. [58].)

Another approach was based on the use of an inner osmotic pressure to push out the plug from the insoluble capsule thus allowing drug release after the lag time. The Port® system was composed of a gelatin capsule coated with a semipermeable membrane (e.g., cellulose acetate), which was filled with an osmotic charge and closed with an insoluble plug (e.g., lipids such as Gelucire®).[60] In contact with aqueous media, water diffused across the semipermeable membrane, resulting in a higher inner pressure and ejection of the plug after a certain lag time, which was mainly controlled by the coating thickness of the semipermeable membrane. The system was already tested in a human study, showing good agreement between lag times measured in vivo and in vitro.[61] An additional immediate or sustained release dose could be placed between the soluble gelatin cap and the insoluble plug.

In the Chronset® system (Fig. 11), the driving force for the drug release was an osmotically active layer in the

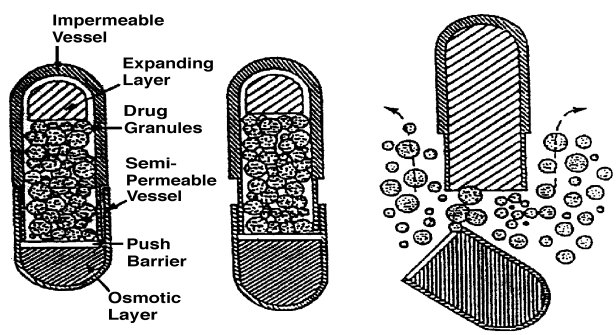

Fig. 11 The Chronset® system. (From Ref. [61].)

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semipermeable vessel, which pushed the cap out off the impermeable vessel after a predetermined time interval.[62] The complete release of the drug, often problematic in capsular-shaped dosage forms, was ensured by an expanding layer at the bottom of the capsule body.

Even more sophisticated were insoluble high-frequency (HF) capsules, which released the drug in a pulsed fashion after a high-frequency signal was applied externally to the human body.[63,64] These HF capsules were used to evaluate the absorption of drugs from distinct regions within the digestive tract. A similar capsule activated by an oscillating magnetic field has been published recently, which ejected an active compound or a radioactive marker to localize the position of the dosage form in the gastrointestinal tract.[65]

In general, the large-scale manufacturing of the abovementioned capsular-shaped pulsatile drug delivery systems appears to be complicated. Special equipment and several manufacturing steps are necessary to combine all components.

CONCLUSION

The use of pulsatile drug delivery system should be taken into consideration for drugs with a chronopharmacological behavior, a high first-pass effect, the requirement of night time dosing or site-specific absorption in the GI-tract. In recent years, a wide variety of interesting single and multiple unit systems have been developed for oral application. However, many systems are only of academic use because of their complex manufacturing process or nonapproved excipients. Most systems perform quite well in vitro, but their performance in vivo has often not been tested. One major challenge will be to obtain a better understanding of the influence of the biological environment on the release performance of pulsatile delivery system in order to develop simple systems based on approved excipients with a good in vitro/in vivo correlation.

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